**Novel Technologies for *in Vivo* Imaging**

This program announcement (PA) must be read in conjunction with the current Omnibus Solicitation of the NIH, Centers for Disease Control and Prevention, and Food and Drug Administration for Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) grant applications. The solicitation (http://grants.nih.gov/grants/funding/sbirsttr1/index.pdf or http://grants.nih.gov/grants/funding/sbirsttr1/index.doc) contains information about the SBIR and STTR programs, regulations governing the programs, and instructional information for submission. All of the instructions within the current SBIR/STTR Omnibus Solicitation apply.

The NIEHS, the National Cancer Institute (NCI), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the National Institute of Neurological Disorders and Stroke (NINDS) invite applications for the development and delivery of novel *in vivo* image acquisition or enhancement technologies, methods for biomedical imaging, and image-guided interventions and therapy. Applications may incorporate limited pilot or clinical feasibility evaluations using either preclinical models or clinical studies. This initiative is primarily intended to facilitate the proof-of-feasibility, development, and delivery of novel imaging technologies for early detection, screening, diagnosis, image-guided interventions, and treatments of various diseases, and, secondarily, to facilitate limited evaluation studies to show proof of concept and functionality.

The interests of the NIEHS focus on detection of intracellular events including gene expression and signal transduction pathway alterations, and screening or diagnosis of tissue and organ toxicities related to exposures to environmental agents. These areas of interest include initiation of toxicity or exacerbation of disease or dysfunction resulting from toxic exposure, treatment, and recovery. The interests of the NCI focus on imaging *in vivo* for cancer preconditions, cancer screening, diagnosis, progression, treatment monitoring, recurrence, and image-based surrogate end points. The NCI's interests include development and delivery of imaging technologies that are cancer-specific, and optimization and validation of imaging technologies for cancer applications. The scope includes system integration, contrast agents, pre- and postprocessing algorithms and software for imaging, image understanding, and related informatics that are cancer-specific. The interests of the NIDDK focus on diabetes mellitus and digestive and kidney diseases. The interests of the NINDS focus on development and delivery of neuroimaging technologies that can be applied to diagnosis and treatment of neurological disorders.

This PA is directed toward the development, optimization, and delivery of innovative image acquisition and enhancement methods, including high-risk/high-gain research on technologies such as 1) novel single- and multimodality molecular imaging systems, methods, agents, and related software and informatics, including the integration of these technologies with emerging biomedical imaging methods for more effective health care delivery for cancer and other diseases; and 2) novel single- and multimodality anatomical and functional imaging systems, methods, agents, and related software and informatics for more effective health care delivery for cancer and other diseases. In addition, research partnerships among investigators in both academia and device and drug industries are encouraged to more rapidly translate and deliver completed imaging system developments.

This PA will utilize the SBIR/STTR mechanisms but will be run in parallel with an NCI PA of nearly identical scope, PA-04-095 (http://grants.nih.gov/grants/guide/pa-files/PA-04-095.html), that utilizes the phased innovation award (R21/33) and the R33 mechanisms for exploratory and developmental studies, and which is open to a broad range of organizations. Fast-track applications are encouraged in this solicitation because they benefit from expedited evaluation of progress following phase I exploratory/feasibility work for immediate decision on transition to phase II funding for expanded developmental work.

The overarching research objectives of this PA are to stimulate development, optimization, and delivery of novel imaging technologies and methods to capture, process, validate, present, interpret, or understand *in vivo* imaging data that support the missions of one or more of the institutes involved.

Significant advances in medical imaging technologies have been made over the past 25 years in such areas as magnetic resonance imaging (MRI), computed tomography (CT), nuclear medicine, ultrasound, and optical imaging. These advances largely focused on structural or anatomical imaging at the organ or tissue level. Now there is an opportunity to stimulate the development and integration of novel imaging technologies that exploit our current knowledge of the genetic and molecular bases of various diseases. Molecular biological discoveries have great implications for prevention, detection, and targeted therapy. Imaging technologies that can provide similar kinds of cellular and molecular information (that is, *in vivo* molecular imaging) to those currently available from histological or microarray techniques used for *in vitro* studies would be very useful.

The advances in molecular methods pose new requirements for the performance of conventional biomedical imaging systems. For example, molecular imaging systems may need to be optimized for a molecular probe (or probes) as well as for anatomical imaging. The integration of molecular imaging methods into multimodality systems will affect data acquisition, processing, reduction, display, and archiving. Therefore, there is a need to support advances in methods for both molecular and conventional anatomical and functional imaging.

The need to encourage and support biomedical imaging and imaging technology development by academic and industrial researchers includes 1) promoting the development of novel high-risk/high-gain technologies; 2) supporting these technologies to maturation, dissemination, and full exploitation; 3) integrating new technologies into commercially available imaging systems for targeted applications; 4) harmonizing imaging methods across versions of a single platform or across multiple platforms to permit the image-based surrogate outcome metrics of the kind required for multisite preclinical and clinical investigations; 5) funding a small number of copies of integrated system prototypes for placement, as required, for off-site research and clinical feasibility studies; and 6) improving technology transfer, delivery, and dissemination by promoting early-stage partnerships between academia and industry to encourage sharing of research resources, including data sharing and validation studies necessary to meet federal regulatory requirements. Therefore, the aims of this initiative and the support mechanism are also directed at encouraging the development and delivery of imaging tools to support biomedical imaging in general for applications in oncology and other diseases.

Development of novel imaging technologies usually requires multidisciplinary approaches and teams with broad expertise in a variety of research areas. Such varied expertise might include imaging physics, chemistry, molecular and cellular biology, signal and image processing, computer vision, informatics and biostatistics, and clinical sciences. The coordination and collaboration of investigators with the necessary variety of disciplines to demonstrate the utility and applicability of new imaging methods is encouraged.

The purpose of this initiative is to facilitate the development of novel imaging technologies for risk assessment, early detection, screening, diagnosis, or image-guided treatment of cancer and other diseases and to facilitate clinical evaluation and optimization studies that are specifically limited to proof-of-concept and pilot data on clinical functionality of the development. Clinical trials for clinical validation of emerging imaging technologies are beyond the scope of and not responsive to this PA.

Studies with preclinical models and clinical studies to demonstrate the feasibility of developments are encouraged, including multisite evaluations, where appropriate. Methods that establish "ground truth" are required at appropriate levels of resolution to validate these emerging imaging methods, such as imaging excised tissue using protocols similar to those used *in vivo*, or correlation of molecular imaging results with microarray library analyses. Developments of molecular probes or targeted contrast agents are considered important approaches to detection of molecular changes *in vivo* to take better advantage of many technologies with potential for molecular imaging. The following topics would make appropriate proposed projects. This list is not meant to be all-inclusive.

1) *Early disease detection.* Developments may address innovative high-resolution imaging methods, with a particular intent to identify and characterize abnormalities or other early changes, including molecular events on the path to disease. Novel solutions for *in vivo* microscopic imaging systems or microscopic implanted devices with high spatial and/or temporal resolution that may use either intrinsic or exogenous contrast agents.

2) *Disease screening.* These methods may include, but are not limited to, development and optimization of efficient imaging systems for screening, with the intent of achieving improved sensitivity and specificity for disease detection. Applications could address innovative improvements to current imaging methods, including hardware and/or software upgrades, or emerging imaging sensors and methods. Research topics of interest include means to significantly reduce imaging time or effects of motion, use of novel contrast agents or imaging probes, and use of technologies that reduce or do not involve the use of ionizing radiation or contrast agents and imaging probes. System integration and software methods could include a variety of image processing and data reduction techniques including temporal analysis of serial studies, close-to-real-time image processing, novel image display methods, and related imaging informatics for more cost-effective solutions for screening.

3) *Imaging for diagnosis, staging, or monitoring the effects of therapy.* This initiative encourages, but is not limited to, the development of novel imaging methods such as functional or molecular imaging or spectroscopy methods that would significantly improve the specificity of diagnosis of cancer and other diseases, allow deterministic methods or patient-specific staging, or measure early effects of therapy. Examples of system integration would include multimodality imaging, image fusion or registration of the different modalities employed, development of software methods that would estimate the probability of malignancy or other specific disease identification, quantitative information for

monitoring the effects of therapy, and close-to-real-time image analysis.

4) *Image-guided biopsy (IGB), image-guided therapy (IGT), and image-guided interventional (IGI) procedures.* This initiative encourages novel approaches using imaging technologies needed to significantly improve specificity, identify lesion extent and microscopic involvement, and minimize tissue damage accompanying biopsy and therapy. Of particular interest are innovative approaches to IGB, IGT, or ITI methods that include novel imaging systems that provide molecular target information or information at the cellular or molecular level sufficient for image guidance and treatment. Examples of system integration that are of interest include, but are not limited to, multimodality imaging, navigational systems, registration methods, real-time feedback mechanisms for controlling therapy (including radiation therapy), computer-assisted surgery, or the use of methods that are adaptive or allow patient-specific optimization of treatment.

5) *Copies of prototype imaging systems.* Support may be requested to make one or more copies of the prototype for placement in collaborating facilities for research purposes, namely preclinical or clinical feasibility investigations, including harmonization across versions of a single platform or across multiple platforms to enable multicenter comparison studies. There is the possibility for collaboration with NCI-funded centers such as the NCI Network for Translational Research in Optical Imaging or the Lung Image Database Consortium.

6) *Research resources.* Development of publicly accessible research resources that facilitate a consensus process for optimization and validation of emerging imaging technologies is encouraged. Examples include the development of open source software, image processing software, and related informatics that can be ported onto different platforms, methods and image databases required for validation of software performance, and other hardware or informatics methods that assist in more efficient delivery of imaging technologies for screening, diagnosis, and treatment for cancer and other diseases.

The SBIR/STTR Omnibus Solicitation indicates the statutory guidelines on levels of funding support and periods of project duration for SBIR and STTR phase I and phase II awards. For this PA, budgets up to $1 million total costs per year and time periods up to 3 years for phase II competing continuations for NCI and NINDS grantees may be requested. For phase I/phase II fast-track applications, the total duration of support cannot exceed 5 years.

Applications submitted in response to this PA will be accepted by 1 August 2004, 1 December 2004, or 1 April 2005. More information on this PA is available online at http://grants1.nih.gov/grants/guide/pa-files/PA-04-094.html. The PHS 398 research grant application must be used for all SBIR/STTR phase I, phase II, and fast-track applications (new and revised).

Effective 1 October 2003, applications must have a Dun and Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the universal identifier when applying for federal grants or cooperative agreements. The DUNS number can be obtained by calling 1-866-705-5711 or through the D&B website at http://www.dunandbradstreet.com/. The DUNS number should be entered on line 11 of the face page of the PHS 398 form. The PHS 398 is available at http://grants.nih.gov/grants/funding/phs398/phs398.html. Prepare your application in accordance with the SBIR/STTR Omnibus Solicitation and PHS 398. Helpful information for advice and preparation of the application can be obtained at http://grants.nih.gov/grants/funding/sbirgrantsmanship.pdf.

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**Epidemiology and Other Health Studies Financial Assistance Program**

The Department of Energy (DOE) Office of Environment, Safety, and Health announces the availability of funds to provide medical evaluations in order to identify occupationally related health impacts in former DOE workers. This request for applications (RFA) is a follow-up announcement to a more general annual notice of potential availability of grants and cooperative agreements for epidemiologic and other health studies published in the *Federal Register* (60 FR 50561) on 29 September 1995.

The DOE is seeking applications for a cooperative agreement to fund a medical evaluation program that will serve all former DOE workers nationwide and will incorporate activities currently performed under the Former Worker Medical Screening Program and the Former Beryllium Worker Medical Surveillance Program. It is anticipated that a single award will be made to fund all of these activities.

The Former Worker Medical Screening Program was initiated in 1996 to provide targeted medical screening to former workers subject to health risks as a result of their employment at the DOE's defense nuclear facilities. Since its inception, medical evaluation based on worker exposure has been offered to former workers through 15 projects at 12 DOE sites. To date, more than 215,000 former workers have been invited to participate, approximately 35,000 have indicated interest in participating, and approximately 25,000 have been screened. Information collected is being used both to improve safety and health practices for current and future DOE workers and to assist the DOE in its administration of subtitle D of the Energy Employees Occupational Illness Compensation Program Act.

Another component of the program funded through this cooperative agreement will be the activities previously conducted by the DOE's Former Beryllium Worker Medical Surveillance Program, which offers medical testing for beryllium sensitivity and chronic beryllium disease (CBD) to former employees who were potentially exposed to beryllium as a result of their work at various DOE sites not initially covered by the Former Worker Medical Screening Program. To date, more than 75,000 former beryllium workers have been invited to participate, approximately 25,000 have indicated interest in participating, and approximately 21,000 program participants have been screened.

The DOE intends to award one cooperative agreement with a number of specific goals, which include 1) development of efficient methods for contacting and informing former DOE workers about the provisions of this program; 2) establishment of an effective communication system (including, for example, a toll-free number, a webpage, and other resources) that former workers may use to contact the program to ask questions and/or arrange for medical evaluation related to their DOE work, and that will serve as a resource and referral service to specialty physicians when appropriate; 3) provision of a one-time medical evaluation following medical protocol and based on a participant's personal work history (in some cases, a literature review of the exposures potentially associated with specific sites may be useful)—in order to maximize the usefulness of these examinations in detecting conditions with latency periods, the program should focus on potential participants who separated from the DOE before 1998, and symptomatic individuals should enroll as soon as possible; 4) communication of information to former workers regarding the nature of their health risks and recommendations for follow-up, based on test results; 5) provision of a follow-up beryllium sensitization blood test for a symptomatic individual upon request or to an otherwise concerned individual at no greater frequency than once every three years; 6) use of local physicians (especially the participants' personal physicians, when available) to provide these medical evaluations—orientation and education of local physicians regarding the use of the program's medical protocol will be provided as necessary; 7) use of physicians and other health care professionals who are appropriately licensed in the state(s) in which they practice and maintain adequate professional liability insurance; 8) provision of logistical assistance and reimbursement of travel costs to the small number of participants who may have to travel more than 150 miles each way to receive their evaluation (specific details will be decided in conjunction with the DOE program manager); 9) distribution of a DOE-provided flyer with information on various worker compensation alternatives; 10) establishment of quality assurance measures to ensure that program services are delivered according to protocol and verify that all laboratories and radiology facilities used are appropriately certified; 11) submission of detailed monthly financial and quarterly progress reports to the DOE (reporting format and content to be specified) and participation in periodic meetings (approximately one per year) and monthly conference calls with the DOE regarding project status; 12) compliance with the Health Insurance Portability and Accountability Act of 1996 and all relevant portions of the Privacy Act; 13) compliance with DOE data disposition requirements upon project completion; and 14) evaluation of former workers' satisfaction with the project medical services using an acceptable patient satisfaction survey such as those developed for the Johns Hopkins Health Center or the Mayo Clinic.

Subject to fiscal year 2005 congressional appropriations, the maximum amount for a single award made under this announcement is expected to be $6 million per year or $30 million total, and the minimum amount for a single award is expected to be $4 million per year or $20 million total. The actual level of funding will be based on the application selected and the appropriations received. Applications must be prepared using the SF 424 form. The SF 424 form is available at http://professionals.pr.doe.gov/ma5/ma-5web.nsf/FinancialAssistance/IIPSFAForms?OpenDocument. Applications must be received by 30 June 2004.

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